UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,032	01/03/2001	Matthew P. Scott	CIBT-P10-203	2036

28120 7590 02/09/2004

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
BRANNOCK, MICHAEL T	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,032	SCOTT ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *083001, 100702,*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed 11/10/03. Additionally, Applicant is reminded that the instant claims 20 and 21 will be examined only to the extent that they read of the elected group of assays utilizing the human patched gene.

Applicant traverses the restriction between screening methods using patched from different species on the basis that the subject matter overlaps and each group is classified together. This argument has been fully considered but not deemed persuasive. Each patched protein is a distinct molecule and would require it's own search. Although a search of any one of the groups may overlap that of another, the search of one group could not be relied upon, solely, to provide art that is anticipatory or would render obvious the invention of any other group, and to search all groups would be burdensome. Therefore, the restriction is maintained and made FINAL.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or

continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons.

Claims 20 and 21 require a "patched protein". The recited term "patched protein", without reference to a specific sequence identifier, is indefinite because the instant specification does not identify that material element or combination of elements which is unique to, and therefore, definitive of "a patched protein". An artisan cannot determine what limitations are placed upon a claim by the presence of this term.

In the preamble of claim 20 and 21, the phrase "the patched protein" lacks antecedent basis in the claim, therefore the artisan could not know which patched protein is *the* patched protein.

Similarly, in line 3 of claim 20, the phrase "the candidate protein" lacks antecedent basis.

Claim 20 depends on claim 1 for the term "a DNA sequence according to claim 1", yet it is unclear which DNA sequence of claim 1 that claim 20 refers to, because claim 1 does not appear to make sense grammatically, i.e., the examiner cannot decipher the meaning of the phrase "of at least about 12bp different from the sequence of the Drosophila patched gene".

Claim 21 requires a transcriptional initiation region consisting of a marker gene and a transcriptional termination region. The artisan would not know what this means, there do not appear to be any such transcriptional initiation regions known in the art, and nor has any been described in the specification. For this examination, however, it will be assumed that it is intended that it is the "expression cassette" that is meant to consist of these elements.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for assays of a patched protein that binds a naturally occurring hedgehog protein, wherein the patched protein is encoded by a DNA sequence which encodes a naturally occurring patched protein, and wherein the cell of claim 21 is an invertebrate cell and wherein the transcription initiation region is a 5' noncoding region of an invertebrate patched gene, does not reasonably provide enablement for non-naturally occurring patched proteins, nor assays in other than invertebrate cells and invertebrate promoters requiring patched induced gene activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses full-length proteins and encoding nucleic acid sequences for human, mouse, Drosophila, and butterfly patched proteins. Partial sequences are provided for mosquito and beetle. In addition, methods of isolating other naturally occurring patched proteins

are provided and include specific PCR primer and disclosed sequences functional as probes that can be used for isolation of encoding DNAs from sources of naturally occurring nucleic acids. One of skill in the art would reasonably expect that patched proteins derived form natural sources would inherently possess the required structural and functional characteristics which allow the proteins to couple to downstream effectors - which is required of the claimed method. However, there is no teaching of a non-naturally occurring patched protein. There is no disclosure of required structural relatedness between non-naturally and naturally occurring patched proteins. In the absence of these, it would require undue experimentation to determine which amino acid sequence variants of naturally occurring patched proteins, or which post-translational modifications to patched proteins could be made that preserve the required structural/functional properties of naturally occurring patched proteins

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond

the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants of patched proteins that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Additionally, claim 21 requires the use of patched signaling-responsive promoters in vertebrate cells, yet none are described and none are known in the art. At pages 12 and 18 the specification describes experiments wherein a reporter gene comprising Drosophila 5' untranslated patched gene DNA was activated by the presence of Drosophila patched expressed in a Drosophila cell, yet the specification provides no guidance as to any vertebrate 5' untranslated regions that are sufficient to drive the expression of a reporter gene in response to a vertebrate patched protein expressed on the surface of a vertebrate cell. Applicant has identified certain stages of the Drosophila embryo wherein the Drosophila reporter construct works in response to a Drosophila patched protein, however, one of skill in the art appreciates that patched proteins are important regulators of embryonic development, and as such, one would not expect that a Drosophila patched reporter construct would function as required in an organism as

morphologically and evolutionarily distant as a human - as is required by the claims. Nor would it be expected that a human patched protein would function in the assay system disclosed in the specification. According to the specification, the patched protein is a membrane protein, the activity of which drives its own expression. Consequently, it is well appreciated that there must be at least one, possibly many, proteins or second messengers that convey the signal from the patched protein in the membrane to the nucleus of the cell. One would expect that the appropriate signal transducing molecules for the Drosophila assay system might be present in a Drosophila embryo, yet the specification has provided no guidance that factors required to drive the expression of a Drosophila construct are present in a vertebrate cell, nor which of the multitude of vertebrate cells might contain factors required for the expression of a vertebrate construct. To create such a vertebrate construct and to find such cells, if in fact they exist, would be burdensome. Aguirre, A. et al, Biotecnologia Aplicada 13(1)32, 1996 attempted applicant's experiment with the Drosophila patched promoter in transgenic mice. Some mild blue staining was observed in certain brain and spinal chord regions, yet the meaning could not be discerned because staining was also seen in controls (see the last paragraph). The skilled artisan, would understand from this experiment that it would not be a straight forward matter to find cells in vertebrate animals so as to be able to use them to screen for compounds that bind patched and activate a reporter construct as is required by the claims. The specification has failed to teach which non-invertebrate cell types possess the required molecular machinery to be used as the claims require.

Due to the large quantity of experimentation necessary to generate the infinite number of variants of naturally occurring patched proteins encompassed by the claims and possibly screen

same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by Forbes-AJ et al., Development 1993 Supplement, pages 115-124.

Forbes-AJ et al., disclose Drosophila embryos made transgenic with a patched promoter LacZ construct that wherein the LacZ reporter gene is under the control of the activity of the patched protein expressed on the cell and is a measure of the binding to and activation of compounds that bind to the patched protein. The skilled artisan appreciates that the Forbes et al. used these cells in a method for screening candidate compounds, e.g. endogenous hedgehog compounds for the ability to bind to and activate patched (see the Abstract and page 117).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (571) 272-0871.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

February 7, 2004

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600